

Safety and outcome of external beam radiation and neutron brachytherapy in elderly patients with esophageal squamous cell cancer

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Abstract

Purpose: The aim of this study was to retrospectively observe and analyze the long-term treatment outcomes of 191 elderly patients with esophageal squamous cell cancer (ESCC) who were treated with californium-252 (²⁵²Cf) neutron brachytherapy (NBT) in combination with external beam radiotherapy (EBRT).

Material and methods: From January 2002 to November 2012, 191 patients with ESCC underwent NBT in combination with EBRT. The total radiation dose to the reference point via NBT was 8-25 Gy-eq in two to five fractions with one fraction per week. The total dose via EBRT was 50-60 Gy, which was delivered over a period of 5 to 6 weeks with normal fractionation.

Results: The median survival time for the 191 patients was 23.6 months, and the 5-year rates for overall survival (OS) and local-regional control (LRC) were 28.7% and 54.2%, respectively. The patients' age was a factor that was significantly associated with OS ($p = 0.010$), according to univariate analysis. The 5-year OS (LRC) was 37.3% (58.6%) for patients aged 70-74 years and 14.5% (47.9%) for patients aged > 74 years ($p = 0.010$ and $p = 0.038$). In multivariate analysis, age and clinical N stage were associated with OS and LRC ($p = 0.011$ [0.041] and $p = 0.005$ [0.005]). From the time of treatment completion to the development of local-regional recurrence or death, 5 (2.6%) patients experienced fistula and 15 (7.9%) experienced massive bleeding. The incidence of severe late complications was related to older age ($p = 0.027$), higher NBT dose/fraction (20-25 Gy/5 fractions), and higher total dose (> 66 Gy).

Conclusions: The clinical data indicated that NBT in combination with EBRT produced favorable local control and long-term survival rates for elderly patients with ESCC, and that the side effects were tolerable. Patient's age, clinical stage N status, and radiation dose could be used to select the appropriate treatment for elderly patients.

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Key words: californium-252, elderly patients, esophageal squamous cell cancer, neutron brachytherapy, late complication.

Purpose

In 2015, an estimated 477.9/100,000 cases of esophageal cancer (EC) were diagnosed in China, and approximately 375/100,000 people died from this disease [1,2]. In China, EC occurs in 50.3% (161.3/320.8) of patients' aged 60-74, and in 19.6% (62.9/320.8) of patients over 75 years of age in [1,2]. A radiation therapy oncology group study (RTOG 8501) demonstrated a survival benefit of the addition of platinum-based chemotherapy to radiation, compared to radiation alone for patients with nonsurgical EC [3,4]. RTOG 8501 only included about 23.1% (28/121) of elderly patients (≥ 70 years). Thus, management of elderly patients with EC remains a therapeutic challenge,

and the most relevant treatment modalities are still being debated. Although survival improvement has been observed over the past decade, EC treatment continues to be significantly influenced by age [5]. Moreover, it has also been reported that elderly patients have undergone less surgery, radiotherapy, and chemotherapy than younger patients [6]. To our knowledge, no specific data have been published regarding therapeutic strategies in elderly patients with EC. Despite progress in surgical practice, esophagectomy is associated with significant morbidity and mortality, and 75 years is often considered as the age limit for surgery [7]. External beam radiation therapy (EBRT) was an important treatment strategy for elderly patients. However, a few published results indicate that

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EBRT combined with brachytherapy in elderly patients with EC. Californium-252 (^{252}Cf) is a neutron-emitting radionuclide, and ^{252}Cf -based neutron brachytherapy (NBT) has only been implemented in China very recently [8]. Neutron brachytherapy is a form of high linear energy transfer (LET) radiotherapy, which has been proven to be effective for treating intracavitary cancers of the cervix when used in combination with EBRT [9,10].

We performed a retrospective cohort study of 191 patients older than 69 years who were diagnosed with locally advanced esophageal squamous cell cancer (ESCC), treated with radiation therapy. The main objective was to assess the overall survival and local control rates after EBRT plus neutron brachytherapy for elderly ESCC patients. We also evaluated the impact of age on treatment tolerance, prognostic factors, and patterns of failure.

Material and methods

Patients

From January 2001 until November 2012, a total of 191 consecutive patients older than 69 years with localized, advanced ESCC were referred to our department at the Changzhi Cancer Hospital for radiotherapy and ^{252}Cf NBT. The reasons were as follows: 30 patients were medically inoperable (6 patients were diabetic, 11 had chronic obstructive pulmonary disease, and 13 patients had a prior or concurrent malignancy); 34 patients rejected surgery; 76 patients were too old (75 years or older, 33 of 85 had T4 lesion); and 85 patients had unresectable lesions. Of these, 191 patients were treated with EBRT combined with brachytherapy. Patients with good performance status (at least able to care for himself or herself) and adequate hepatic, renal, and hematologic functions were selected for curative treatment. All the patients had squamous cell carcinoma. The patients' clinical stage was diagnosed by barium examination, endoscopy, endoscopic ultrasonography, or tumor histology.

Radiotherapy

Megavoltage radiation therapy units were used with a minimum source-to-axis distance of 100 cm. The radiation field extended at least 3 cm superior and inferior to the tumor, with a lateral margin of at least 2 cm. The field included the lesser curvature and bottom of stomach if the tumor invades gastroesophageal junction. The boost radiation field was the same length. Multi-field techniques were used to limit the maximum dose to the spinal cord to ≤ 45 Gy. The radiation treatments were delivered 5 days/week at 2 Gy/fraction. The initial anterior-posterior parallel-opposed fields received 30 Gy, and the off-cord fields received 20-30 Gy, for a total dose of 40-54 Gy in 20-27 fractions in 4-5.5 weeks.

Neutron brachytherapy with a one-balloon applicator (Figure 1) [11] was used in conjunction with the ^{252}Cf LZH-1000 remote after-loading system (Linden Science and Technology Co., Shenzhen, China). The physical characteristics of the ^{252}Cf neutron, the characteristics of the applicator, and the process of NBT were described in detail by Liu [12,13]. The NBT dose was prescribed to

the reference point, which was located at 10 mm from the center point of the source capsule in the transverse direction. Figure 1 is an X-ray image taken while the applicator and the simulator source were both inserted into the esophagus of a patient. The source applicator is a custom-made catheter, which not only allows the source wire to travel inside, but also includes a water balloon surrounding the source. The water balloon is 12 cm long, and its diameter can vary depending on the amount of water injected into it. The water balloon is an essential part of the applicator. For tumors that are eccentric with respect to the axis of the esophagus, the water balloon can be inflated accordingly to keep the source close to the tumor but away from the adjacent normal epithelium. In Figure 1, the water balloon can clearly be seen as it is filled with an X-ray contrast agent. The total NBT dose (to the reference point) given to each patient varied between 8 and 25 Gy-eq in two to five fractions, with 4-5 Gy-eq per fraction per week.

Toxicity assessment and follow-up

The patients were examined weekly during the EBRT. Weekly blood tests were obtained, and any admission for treatment-related complications was recorded. All adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 [14].

The patients usually underwent follow-up examinations every 3-4 months after the completion of treatment. Tumor response and nodal disease were evaluated with repeated computed tomography (CT) scans, barium swallow studies, and endoscopy.

Statistical analysis

The objectives of the study were to evaluate overall acute toxicity and local-regional control rates. Death from ESCC was considered as treatment failure in the survival analysis. Survival was calculated from the date of consultation until death or last follow-up evaluation. The pattern of failure (local and/or regional vs. distant) was defined as the first site of failure. The time to first failure, time to any local failure, and time to any distant metastases were calculated from the date of consultation. Local and regional recurrence included the primary tumor and regional lymph nodes. Overall survival and local-regional control were estimated using the Kaplan-Meier method. The parameters were also analyzed by multivariate analysis using the Cox regression model. Pearson's χ^2 test was used to assess measures of association in the frequency data. A value of $p < 0.05$ was considered statistically significant.

Results

Patients' characteristics and treatments

Age of the ESCC patients who were treated with radiation therapy (NBT and EBRT) ranged from 70 to 84 years (median: 75 years). There were 115 patients aged 70-74, and 76 patients aged > 74 years. The cancer stages were

categorized according to the 6th edition of the AJCC Cancer Staging Manual, with 72 patients categorized as stage IIA, 10 patients categorized as stage IIB, and 109 patients were categorized as stage III. The detailed patient data and log-rank test are provided in Table 1.

Prognostic factors for overall survival and local-regional control

The duration of follow-up ranged from 6 to 106 months (median: 30.4 months). The median survival time for the 191 patients was 23.6 months, and the 1-, 2-, 3-,

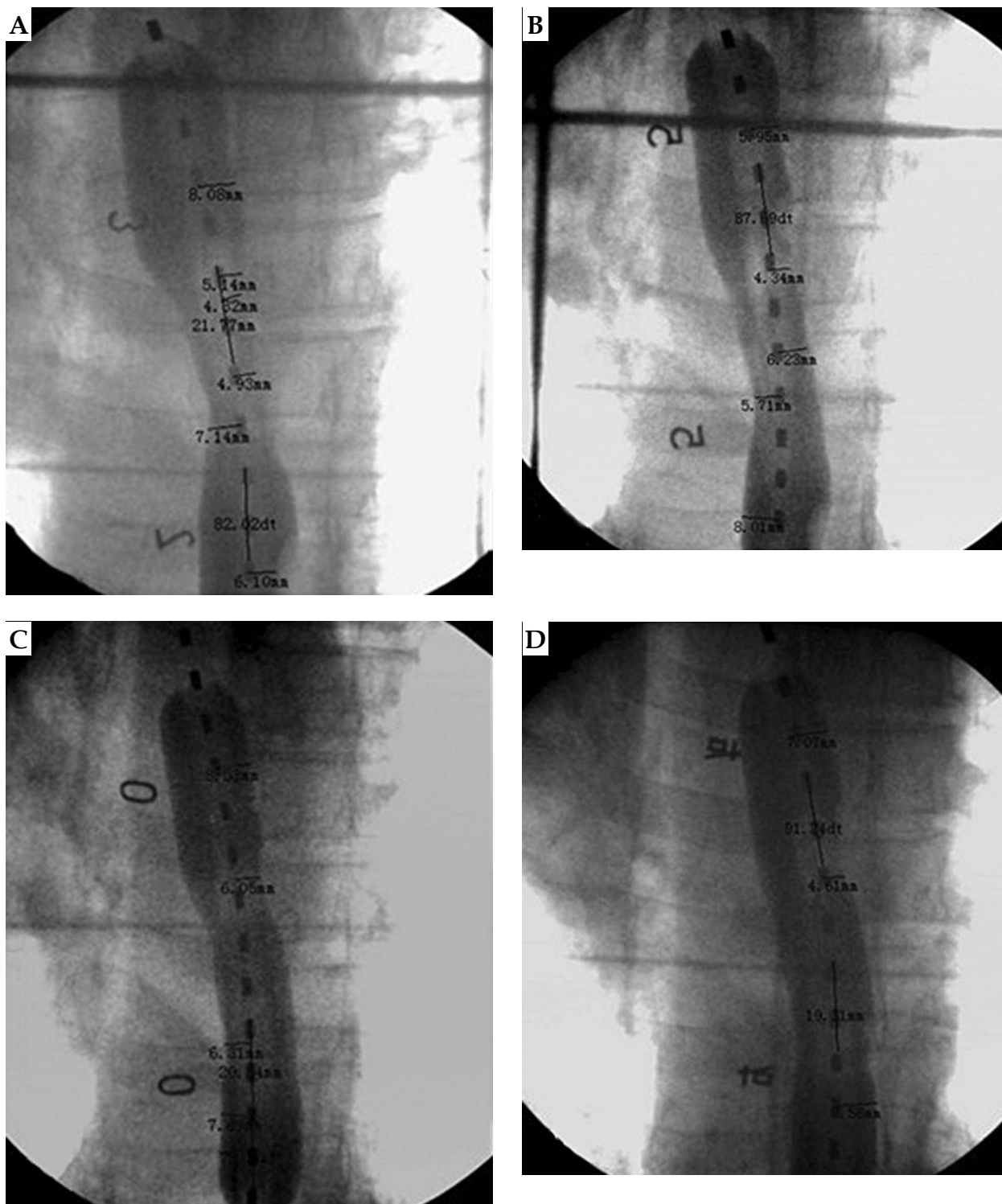


Fig. 1. Images (A-D) showing a 75 years' male patient, middle site esophageal squamous cell cancer. The length of primary tumor is 6 cm. The tumor regression conditions before each of the four neutron brachytherapy treatments under an X-ray treatment-planning simulator from A-D

Table 1. Patient and tumor characteristics

Characteristics	Total (%)	70-74 years (%)	> 74 years (%)	<i>p</i> value
Gender				0.550
Male	103 (53.9)	60 (52.2)	43 (56.5)	
Female	88 (46.1)	55 (47.8)	33 (43.5)	
KPS				0.001
≥ 80	90 (47.1)	65 (56.5)	25 (32.9)	
70	101 (52.9)	50 (43.5)	51 (67.1)	
The length				0.029
≤ 5.0 cm	99 (51.8)	67 (58.3)	32 (42.1)	
> 5.0 cm	92 (48.2)	48 (41.7)	44 (57.9)	
Tumor location				0.079
Upper	51 (26.7)	37 (32.2)	14 (18.4)	
Middle	123 (64.4)	67 (58.3)	56 (73.7)	
Lower	6 (7.9)	11 (9.5)	6 (7.9)	
T stage				0.098
T2	40 (20.9)	29 (25.2)	11 (14.5)	
T3	66 (34.6)	34 (29.6)	32 (42.1)	
T4	85 (44.5)	52 (45.2)	33 (43.4)	
N stage				0.279
N0	109 (57.1)	62 (53.9)	47 (61.8)	
N1	82 (42.9)	53 (46.1)	29 (38.2)	
6 th AJCC stage				0.810
IIa	72 (30.7)	43 (37.4)	29 (38.2)	
IIb	10 (5.0)	7 (6.1)	3 (3.9)	
III	109 (64.3)	65 (56.5)	44 (57.9)	
RT dose				0.047
≤ 66 Gy	167 (87.4)	105 (91.3)	62 (81.6)	
> 66 Gy	24 (12.6)	10 (8.7)	14 (18.4)	

RT – radiotherapy alone, OS – overall survival rate, LCR – local control rate

and 5-year rates for overall survival (OS) were 68.5%, 48.2%, 40.3%, and 28.7%, respectively. The 1-, 2-, 3-, and 5-year rates for local-regional control (LRC) were 82.2%, 67.0%, 61.8%, and 54.2%, respectively.

We used the following nine factors for the univariate analysis of survival rates and local control rate: sex, age, Karnofsky score (KPS), tumor location, tumor length, tumor T stage, nodal stage, clinical stage, and radiation dose. Among them, three (age, tumor length, and clinical N stage) were found to have relevance to OS ($p = 0.010$, $p = 0.016$, and $p = 0.009$, respectively). Age, clinical N stage, and radiation dose were factors that were significantly related to LRC ($p = 0.038$, $p = 0.014$, $p = 0.014$, respectively). In the univariate analysis, the 5-year OS (LRC) was 37.3%

(58.6%) for patients aged 70-74 years, and 14.5% (47.9%) for patients aged > 74 years ($p = 0.010$ and $p = 0.038$, respectively, Figure 2A and B). In multivariate analysis, age and clinical N stage were associated with OS and LRC ($p = 0.011$ [0.041] and $p = 0.005$ [0.005]) (Table 2).

Patterns of failure

At the time of the analysis, 80 patients were alive and free of disease, and 5 patients were alive with disease evolution. Distant metastases occurred in 37 patients (19.4%). The median time to developing distant metastases was 8.9 months. The main sites of distant metastases were the lung ($n = 9$), liver ($n = 5$), brain ($n = 2$), and bones ($n = 8$). In 14 patients, metastases developed in more than one organ.

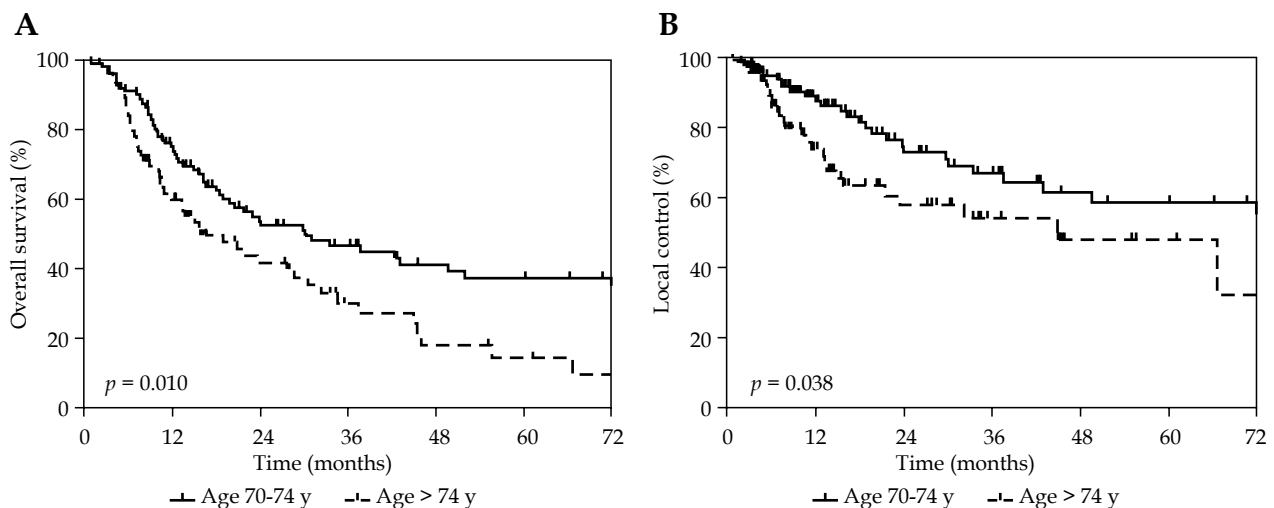


Fig. 2. Comparison of the overall survival rate (A), and local control rate (B) between the two treatment groups

Table 2. Results of multivariate Cox regression analysis of overall survival and local-regional control

Factor	Overall survival			Local-regional control		
	p value	HR	95% CI	p value	HR	95% CI
Age: 70-74 (vs. > 74)	0.011	1.617	1.128-2.476	0.041	1.756	1.024-3.013
Tumor length: ≤ 5 cm (vs. > 5 cm)	0.124	1.357	0.920-2.000	0.570	1.165	0.687-1.976
cN stage: N0 (vs. N1)	0.005	1.762	1.185-2.619	0.005	2.197	1.276-3.782
Total dose: ≤ 66 Gy (vs. > 66 Gy)	0.076	1.569	0.955-2.580	0.011	2.244	1.207-4.171

CI – confidence interval, HR – hazard ratio, c – clinical

Additionally, 15 patients died of mixed causes, including pneumonia, cerebral hemorrhage, and heart infarction. Local-regional recurrence occurred in 59 (59/191, 30.9%) patients, with 9/59 (15.3%) occurrences outside the radiation fields and 50/59 (84.7%) occurrences inside the radiation fields. Additionally, 7/49 (14.3%) had primary tumor recurrences. None of those patients underwent salvage surgery.

Treatment toxicity

In terms of acute toxicity, no perforations were observed during this treatment period. In total, 88 (46.1%) patients developed a grade 2 hematologic toxicity. Dysphagia was relieved after the second or third NBT treatment in 87% of the patients, and a temporary feeding tube was not required in most of the patients. Grade ≥ 2 esophagitis, expressed by clinical odynophagia, was observed in 64 cases (33.5%), and it was managed with the early introduction of H₂ blockers and surface anesthesia at the initiation of the NBT. In total, eight (4.2%) patients had grade ≥ 2 irradiation dermatitis. From the time of treatment completion to the development of local-regional recurrence or death, 5 (2.6%) and 15 (7.9%) patients experienced fistula and massive bleeding, respectively. The median time of incidence was 7.0 (3.7-55.7) months for fistula and 9.5 (3.2-90.9) months for bleeding. As shown in Table 3, the incidence of severe, late complications was

related to older age ($p = 0.027$), higher NBT dose/fraction (20-25 Gy/5F), and higher total dose (> 66 Gy). In total, 68.5% of the patients resumed normal swallowing, while 4.2% had some residual dysphagia (non-malignant) requiring intermittent dilatation.

Discussion

To our knowledge, this is the first reported clinical experience of the treatment using NBT and EBRT for elderly patients with ESCC. The safety and efficacy of this comprehensive treatment appear promising. We also found that, firstly, NBT + EBRT is safe and beneficial in terms of local control in the radical treatment of elderly patients with ESCC, and secondly, the OS rate was significantly increased, and the late complication rate was significantly decreased in patients aged 70-74 years compared to that of patients aged > 74 years. During the treatment period, no severe treatment related complication occurred.

Definitive conformal radiotherapy (CRT) is considered a feasible nonsurgical treatment in patients with a locally advanced EC, and approximately a 50-65% clinical complete response rate, 17-26 months of median overall survival, and 30-40% 2-year survival rate [15,16,17]. In the current study, the OS was similar to the results of prior studies, though without chemotherapy [15,16,17].

We believe that there are at least two factors that made the ²⁵²Cf-based NBT more effective for local tumor than

Table 3. Treatment toxicity and the sites of the first failure according to different age groups

Characteristics	70-74 years (n = 115)	> 74 (n = 76)	p value
Acute toxicity (Events of any grade during treatment – no. of patients; Events of grade ≥ 2)			
Esophagitis	63 (54.8%)	47 (61.8%)	0.631
Skin complications	17 (14.8%)	16 (21.1%)	0.262
Pulmonary complications	5 (4.3%)	3 (3.9%)	0.892
Leukopenia	52 (45.2%)	36 (47.4%)	0.982
Neutropenia	40 (34.7%)	23 (30.3%)	0.849
Thrombocytopenia	13 (11.3%)	6 (7.9%)	0.441
Late toxicity			
Esophageal fistulas	1 (0.9%)	4 (5.3%)	0.063
Massive bleeding	5 (4.3%)	10 (13.2%)	0.027
The sites of the first failure in the whole group			
Local-regional failure	32 (27.8%)	27 (35.5%)	0.045
In field	29 (25.2%)	21 (27.6%)	0.134
Out field	3 (2.6%)	6 (7.9%)	0.032
Distant metastasis	21 (18.3%)	14 (13.1%)	0.128
Lung	4 (3.5%)	5 (6.6%)	0.483
Liver	1 (0.9%)	1 (1.3%)	0.393
Bone	5 (4.3%)	3 (3.9%)	0.483
Brain	1 (0.9%)	1 (1.3%)	0.552
≥ 2 Metastasis sites	10 (3.6%)	4 (5.2%)	0.726
Not otherwise specified (disease of heart, head blood-ves-sel, pneumonia, second tumor)	5 (4.3%)	6 (17.9%)	0.690

Table 4. Comparative toxicity rates, overall survival and local control of selected series

Factor	Hishikawa <i>et al.</i> [20]	Flores <i>et al.</i> [21]	Hareyama <i>et al.</i> [22]	Sharma <i>et al.</i> [23]	RTOG9207 [19]	Present study*
No. of pts.	148 (66# pts)	145	161	100	50	191
BT Gy/fraction	12/2	15/1	15-20/NS	15-20/1	15/3	12-25/2-6
ERT Gy/fraction	60/30	40/15	47-70/25-35	50/28	50	40-60
CT (pts)	No	No	No	Yes	Yes	191/191
Fistula (%)	5.3	5	1.2	12	12	2.6
Bleeding (%)	0	11	0	4	NS	7.9
Ulcer (%)	7.1	NS	3	29	NS	2.6
Stricture (%)	10	35	3	16	4	4.2
Death rate (%)	3	0.6	0	4	8	0
OS (%)	37 (2 y) (66# pts)	26 (2 y) 19 (3 y)	43.3 – stage I (5 y), 21.1 – stage II (5 y)	23 (5 y)	48 (1 y)	36.3 (3 y)
LC (%)	64 (2 y) (66# pts)	NS	31.7% (5 y)	NS	58 (1 y)	75.6 (3 y)

CT – chemotherapy, BT – brachytherapy, EBRT – external beam radiotherapy, Pts – patients, y – years, NS – not stated, OS – overall survival, #LD – limited disease, LC – local control

*Brachytherapy applied between EBRT

chemotherapy regimens, particularly in the treatment of locally advanced ESCC. The first factor is related to the high-LET nature of fission neutrons, which made them much more effective (compared to the low-LET X-ray) in killing the hypoxic tumor cells in the locally advanced cancers. The second factor is related to the fact that water is an effective neutron attenuator that can be conveniently injected into the source applicator during treatment to reduce the neutron dose to the nearby normal tissue. Because there is a significant difference in the elasticities of normal tissue and tumor tissue, the proper injection of water into the source applicator can effectively push away the nearby normal tissue while still keeping the tumor tissue close to the source.

Tougeron reported that age > 74 years was associated with worse creatinine clearance ($p < 0.01$) and greater chemotherapy dose reduction at treatment onset due to age ($p < 0.01$), but this had no influence on total CRT dose, or OS [18]. In the current study, the incidence of late severe complications was significantly related to the factors of higher total dose and NBT dose. In addition to the dose factors, the patients' age also significantly increased the incidence of relevant, late complications. While the normally expected side effects (shown in Table 4) seem to be quite acceptable, the number of deaths ($n = 20$ or 10.5%) resulting from fistula, hematemesis, and hemoptysis is high. This may be linked to the late effect of radiation damage, as fatal esophagitis of fistula cases were also observed in the RTOG 92-07 trial where the ^{192}Ir -based high-dose-rate boost dose of 15 Gy in 3 weekly fractions was deemed to be too high [19]. However, they could also have been caused by local recurrences of the cancer. Further CT review is needed to compare the pretreatment tumor length, esophageal tumor wall thickness, and association of tumor with surrounding normal structures with subsequent fistula formation.

The major limitation of our study was that the retrospective analysis might have been based on incomplete medical records. Others restrictions were that the study was conducted in a single institution, small sample size, and the lack of predefined factors determining treatment decisions, which were based only on evaluations by the referral doctor and members of a multidisciplinary team. It should nonetheless be recalled that the aim of the study was to retrospectively identify the parameters to be associated with the key therapeutic decision.

Conclusions

Our results suggest that elderly patients with ESCC could benefit from NBT + EBRT without major toxicities. Patient's age, clinical stage N status, and radiation dose could be used to select the appropriate treatment in an elderly patient.

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Disclosure

Authors report no conflict of interest.

References

- Zeng H, Zheng R, Zhang S et al. Esophageal cancer statistics in China, 2011: Estimates based on 177 cancer registries. *Thorac Cancer* 2016; 7: 232-237.
- Chen W, Zheng R, Baade PD et al. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; 66: 115-132.
- Cooper JS, Guo MD, Herskovic A et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999; 281: 1623-1627.
- Herskovic A, Martz K, al-Sarraf M et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992; 326: 1593-1598.
- Bouvier AM, Launoy G, Lepage C et al. Trends in the management and survival of digestive tract cancers among patients aged over 80 years. *Aliment Pharmacol Ther* 2005; 22: 233-241.
- Steyerberg EW, Neville B, Weeks JC et al. Referral patterns, treatment choices, and outcomes in locoregional esophageal cancer: a population-based analysis of elderly patients. *J Clin Oncol* 2007; 25: 2389-2396.
- Law S, Wong KH, Kwok KF et al. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. *Ann Surg* 2004; 240: 791-800.
- Wang CKCh. Progress in californium-252 neutron brachytherapy. In: Brachytherapy. Kishi K (ed.). *InTech*, Rijeka 2012.
- Maruyama Y, van Nagell JR, Yoneda J et al. A review of californium-252 neutron brachytherapy for cervical cancer. *Cancer* 1991; 68: 1189-1197.
- Lei X, Qian CY, Qing Y, et al. Californium-252 brachytherapy combined with external-beam radiotherapy for cervical cancer: long-term treatment results. *Int J Radiat Oncol Biol Phys* 2011; 81: 1264-1270.
- Buzurovic IM, Hansen JL, Bhagwat MS et al. Clinical implementation of a novel applicator in high-dose-rate brachytherapy treatment of esophageal cancer. *J Contemp Brachytherapy* 2016; 8: 319-325.
- Liu H, Wang Q, Jia X et al. Early-stage esophageal squamous cell carcinoma treated with californium-252 neutron brachytherapy: clinical report on 16 cases. *Tumori* 2013; 99: 172-175.
- Liu H, Wang Q, Wan X et al. Californium-252 neutron brachytherapy combined with external beam radiotherapy for esophageal cancer: long-term treatment results. *Brachytherapy* 2014; 13: 514-521.
- Common Terminology Criteria for Adverse Events VA, 2006: Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf. Assessed: 5 October 2009.
- Bedenne L, Michel P, Bouché O et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFOCD 9102. *J Clin Oncol* 2007; 25: 1160-1168.
- Stahl M, Stuschke M, Lehmann N et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005; 23: 2310-2317.
- Michel P, Adenis A, Di Fiore F et al. Induction cisplatin-irinotecan followed by concurrent cisplatin-irinotecan and radiotherapy without surgery in oesophageal cancer: multicenter phase II FFOCD trial. *Br J Cancer* 2006; 95: 705-709.

18. Tougeron D, Di Fiore FD, Thureau S et al. Safety and outcome of definitive chemoradiotherapy in elderly patients with oesophageal cancer. *Br J Cancer* 2008; 99: 1586-1592.
19. Gaspar LE, Qian Ch, Kocha WI et al. A phase III study of external beam radiation, brachytherapy and concurrent chemotherapy in localized cancer of the esophagus (RTOG 92-07): preliminary toxicity report. *Int J Radiat Oncol Biol Phys* 1997; 37: 593-599.
20. Hishikawa Y, Kurisu K, Taniguchi M et al. High-dose-rate intraluminal brachytherapy for esophageal cancer: 10 years' experience in Hyogo College of Medicine. *Radiother Oncol* 1991; 21: 107-114.
21. Flores AD, Nelems B, Evans K et al. Impact of new radiotherapy modalities on the surgical management of cancer of the esophagus and cardia. *Int J Radiat Oncol Biol Phys* 1989; 17: 937-944.
22. Hareyama M, Nishio M, Kagami Y et al. Intracavitary brachytherapy combined with external-beam irradiation for squamous cell carcinoma of the thoracic esophagus. *Int J Radiat Oncol Biol Phys* 1992; 24: 235-240.
23. Sharma V, Agarwal J, Dinshaw K et al. Late esophageal toxicity using a combination of external beam radiation, intraluminal brachytherapy and 5-fluorouracil infusion in carcinoma of the esophagus. *Dis Esophagus* 2000; 13: 219-225.